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Original Article

Evaluation of Copeptin and High-Sensitivity Troponin I in Early Diagnosis of Acute Coronary Syndrome

Suhaib Saber Asaad [a] *, **Jassim Muhammed Ibrahim**[a]

[a] Physiology, Biochemistry and Pharmacology Department, School of Medicine, University of Kurdistan Hewler, Erbil, Iraq

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* **Corresponding Author**:
suhaib.sabir@ukh.edu.krd

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Abstract: Acute Coronary Syndrome (ACS) is still the main reason of malady and death world-wide, highlighting needs for quick and accurate diagnosis. Biomarkers such as high-sensitivity troponin (HS-troponin) and copeptin have been known to improve early detection. This study aims to evaluate the levels and clinical significance of copeptin and high-sensitivity troponin I in patients presenting with acute coronary syndrome. A prospective observational study enrolled patients presenting with acute chest pain, who were categorized into ACS and non-ACS groups. The relationship between HS-troponin) and copeptin was examined. In the total of 100 subjects included (62 in ACS group and 38 in non-ACS group). Patients with ACS were significantly older (52.6 vs 44.1 years old, $p = 0.0010$) and more often overweight (51.6% vs. 23.7%, $p = 0.0461$). Lipid abnormalities were markedly higher in ACS patients, including elevated total cholesterol (48.4% vs 2.6%, $p < 0.0001$).), low density lipoprotein (37.1% vs 0%, $p < 0.0001$).), lower high-density lipoprotein (93.6% vs 60.5%, $p < 0.0001$).), and high triglycerides (79.0% vs 15.8%, $p < 0.0001$). Clinically, dyspnea (96.8% vs 73.7%, $p = 0.0009$), arm pain radiation (67.7% vs 28.9%, $p = 0.0002$), and nausea/vomiting (59.7% vs 26.3%, $p = 0.0012$) were significantly more common in ACS. However, copeptin levels and the HS-troponin I × copeptin interaction didn't vary significantly between groups ($p = 0.4516$). Similarly, no significant variation was observed across lipid profile. While traditional risk factors, symptoms, and lipid abnormalities were strongly associated with ACS. In conclusion, evaluation of copeptin and HS-troponin I shows a critical knowledge in early acute coronary syndrome triage. However, due to the systemic stress attenuates copeptin specificity, localized reference intervals are recommended for accurate clinical assessment.

1. Introduction

Cardiovascular diseases (CVD) are known as one of the most serious health challenges around the world and the primary leading cause for premature death worldwide [1]. Regardless of its health challenges, these diseases are known to cause economic disability [2]. The imperative of enhancing cardiac care is underscored by alarming projections, for example the cardiovascular mortality is anticipated to rise by 73.4% by 2025, and total cases are projected to increase by 90% between 2025 and 2050 [1, 3]. Among assorted types of cardiovascular diseases, ischemic heart disease is ranked first for being the most common type [4]. Meanwhile, the most common reason for emergency department admissions is acute coronary syndrome (ACS) [5]. ACS spectrum ranges from unstable angina to type 1 myocardial infarction (MI), which is categorized as non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) based on electrocardiographic (ECG) findings [6]. The most recent 'gold standard' for physicians to diagnose acute myocardial infarction (AMI) includes a common of clinical syndromes, ECG morphology (like ST-segment elevation or depression), and

biochemical blood tests, with high-sensitivity troponin (HS-troponin) as a current criterion biomarker [4, 7]. However, HS-troponin has a significant clinical limitation as known as the 'troponin-blind window' [8, 9]. During the first 3 hours after the onset of myocardial injury symptoms, HS-troponin may remain within a normal range or be slightly elevated, creating uncertainty about diagnostic accuracy and delaying critical treatments [10]. To close this gap, scientists have shifted their attention to copeptin, which is a stable peptide obtained from the C-terminal part of pre-pro-vasopressin [11]. Unlike troponin, copeptin is liberated more quickly into the bloodstream right after acute endogenous stress and hemodynamic changes. Its concentration rises sharply, within 2 minutes of symptom onset, which may facilitate earlier diagnosis of AMI [12].

Ischemic heart disease and its acute manifestation, ACS, are the principal contributors to this global health burden [3]**.** The economic consequences are also substantial, with CVD-related costs expected to exceed $1.1 trillion by 2035 and annual expenditures reaching $600 billion [13]. Pathophysiologically, the Fourth Universal Definition of Myocardial Infarction defines AMI as myocardial injury which is evidenced by increased cardiac troponin concentration regarding the clinical hypoperfusion [14]. The classic cause of type 1 of MI is spontaneous event where the breaking open of atherosclerotic plaque rupture, while an unequal of cardiac muscle oxygen supply and need causes second type myocardial infarction [15].

In the past, other enzymes, such as aspartate aminotransferase and lactate dehydrogenase, have been used to diagnose AMI. This period is termed the enzymatic era. Later, in the 1990s, a new marker was introduced, leading to the 'troponin revolution,' which greatly improved the specificity of the diagnosis [18]. Currently, the high-sensitivity cardiac troponin (hs-cTn) assay is accustomed to exclude AMI quickly, termed 0-hour/1-hour testing, by detecting low troponin levels [16-18]. However, one of the major developments in the current AMI research paradigm is the ‘troponin blind window,' the initial 1 to 3 hours during which troponin levels may not be elevated above the diagnostic threshold despite the occurrence of an AMI [8, 9]. This blind window increases the risk of false negatives among patients who present early [10].

Recently, AMI research paradigm has focused on the character of copeptin, a peptide from the C-terminal of damaged cells [19]. Unlike troponin, which is released from damaged cells, copeptin is released in response to the body’s immediate endogenous stress [20]. The concentration of this peptide increases within minutes of the onset of AMI, a feature that makes it a potent marker for early diagnosis, along with the HS-troponin assay [21].

Clinical studies, such as the CHOPIN study, have finalized that the dual-marker strategy (DMS), which combines negative hs-cTn and negative copeptin results upon admission, can achieve a negative predictive value exceeding 99% for eliminating AMI [12]. Furthermore, studies indicate that this approach can reduce emergency department length of stay by an average of 94 minutes [22].

The literature review revealed several important gaps in the present research. First, the main debate is about whether copeptin provides significant value in medical centers that uses hs-cTn. Second, it’s still unclear how these biomarkers perform within specific patient subgroups, especially in older adults and patients with complex and high-risk comorbidities. Finally, the pronounced issue is regional validity; the majority of landmark studies have been carried out in western healthcare settings.

Therefore, the aim of this study is to evaluate if adding copeptin to HS-troponin improves early diagnostic accuracy for adult patients who are presenting to emergency department with sharp chest ache within six hours of symptom onset and who have a high rate of suspicion of ACS.

2. Materials and Methods

2.1. Study Design and Ethical Approval

This study used a case-control design (ACS patients vs non-ACS patients) to assess combined diagnostic efficacy of hs-cTn I and copeptin in advance determination of ACS. This research focused on biomarker evaluation at the time patients presented to the emergency room, which reflects a real-world clinical situation. The data collection process took place between 14 October 2025 and 18 December 2025 at Rizgary Teaching Hospital. This Hospital is a tertiary-level public hospital in Erbil city, Kurdistan region of Iraq.

The ethical approval acquired from the University of Kurdistan Hewler, School of Medicine (Ethical Code: UKH-MP-003, date: November 17, 2025). The study adhered to the STROBE statement guidelines.

2.2. Study Groups

This study includes two main groups: ACS patients' group consisted of 62 subjects (≥18 years old) attended the emergency department with sudden chest ache and suspected ACS within 6 hours of symptom onset. The non-ACS patients' group consisted of 38 subjects (≥18 years old) attended the emergency department complaining sudden chest ache and suspected to have ACS within 6 hours of symptom onset, but after the evaluation, were diagnosed as non-ACS conditions. Participants were allocated to ACS (STEMI, NSTEMI, Unstable Angina) and Non-ACS (other cardiac and non-cardiac chest pain) groups by a specialist physician.

2.3. Eligibility Criteria

Inclusion and exclusion criteria were implemented to reduce potential confounding variables. Inclusion criteria were patients with the age of ≥18 years who attended emergency department with manifestations indicative of ACS, including acute chest pain, radiating pain, or dyspnea. Only those who arrived within 6 hours of symptom onset were included to ensure assessment within the early diagnostic window for biomarkers. Informed consent was obtained from patients or, when necessary, from relatives capable of providing consent.

Exclusion criteria were patients with immediate, clear non-ACS diagnosis upon initial evaluation, like musculoskeletal chest wall pain, or gastrointestinal problems, patients whose blood samples were not obtained due to immediate transfer to the catheterisation lab, and lastly, patients with chronic renal failures or any other conditions that have baseline elevation of biomarkers and complicating ACS vs non-ACS distinction.

2.4. Study Parameters

Demographic data (age, sex, nationality) have been collected, as well as clinical data (time of onset, progression of symptoms, past medical history, smoking status), and body parameters. Body mass index (BMI) was evaluated using WHO criteria. ECG were evaluated by a cardiologist and classified as STEMI, NSTEMI, unstable angina and other abnormalities.

2.5. Biochemical Analysis

Approximately 5mL of vein blood was obtained from each patient at time of arrival in the emergency room (0 hour), before the start of any treatment. Blood samples were collected within 20 minutes of arrival, placed in EDTA and serum separator tubes, centrifuged, and stored at -80°C. Later, lipid profile parameters of total cholesterol, triglycerides (TG), high density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined and stratified into clinical risk categories. To ensure reproducibility, all analyses were completed within 2 weeks using the specified materials. The researchers blinded the laboratory personnel to the patients' final diagnoses.

Serum biomarker levels were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Hs-cTn I was measured utilizing the human hs-cTn-I (SunLong Biotech Co., Ltd.), with an intra-assay coefficient variation of <10% and an inter-assay of <12% using the human copeptin (ELISA Kit, Wuhan Fine Biotech Co., Ltd. Wuhan, China), exhibiting an intra-assay of <8% and an inter-assay of <10%.

2.6. Reference Standard and Diagnostic Classification

The final determination of AMI was based on the Fourth Universal Definition of Myocardial Infarction, which integrates clinical, ECG, and serial cardiac troponin (cTn) levels. At same time, hs-Troponin I was performed.

2.7. Statistical Analysis

Data normality was assessed using Q-Q plots and histograms. Extreme outliers were addressed by replacing them with the upper or lower quartile, as appropriate. General, medical, and lifestyle characteristics of patients with ACS and non-ACS were summarized using descriptive statistics, comprising mean and standard deviation or median and median absolute deviation (MAD) for numerical variables, number and percentage for nominal variables. Comparisons between ACS and non-ACS groups were executed using independent-samples t-tests or Chi-squared tests, as necessary. The normality of the HS-troponin and copeptin interaction, as well as copeptin levels in the study groups, was not confirmed; therefore, non-parametric statistics were applied. Differences in the HS-troponin and copeptin interaction and in copeptin levels between non-ACS and ACS groups were determined by the Mann Whitney U test. As these dissimilarities were not statistically significant, ROC analysis was not performed. The interaction of HS-troponin and copeptin was calculated as the product of their values. Statistically significant set at p-value less than 0.05. All statistical evaluations were accomplished by using JMP® software version 18 (SAS Institute Inc., Cary, NC).

3. Results

Table 1 shows the characteristic features among patients involved in the current study. The mean age of patients with ACS was 52.60 years old, compared to 44.08 years old in the non-ACS group with statistically significant differences between them (p = 0.0010). Regarding sex, males constituted 66.13% of the ACS group and 55.26% of the non-ACS group, but no statistically significant detected between them (p = 0.2772). Similarly, smoking prevalence was nearly identical between the groups (59.68% in ACS vs. 60.53% in non-ACS; p = 0.9330). In contrast, obesity showed a significant difference (p = 0.0461), with overweight individuals more common in the ACS group (51.61%) compared to the non-ACS group (23.68%).

Table 1: General feature of patients with ACS and non-ACS patients.

Characteristics	Study groups		
	Non-ACS (n=38)	ACS (n=62)	P value
Age (mean ± SD)	44.08 ±13.80	52.60 ±11.12	0.0010[a]
Sex			
Male	21 (55.26%)	41 (66.13%)	0.2772[b]
Female	17 (44.74%)	21 (33.87%)	
Smoking			
No	15 (39.47%)	25 (40.32%)	0.9330[b]
Yes	23 (60.53%)	37 (59.68%)	
Obesity (BMI)			
Normal	18 (47.37%)	12 (19.35%)	0.0461[b]
Overweight	9 (23.68%)	32 (51.61%)	
Obese	11 (28.95%)	18 (29.03%)	

[a] Independent t-test and [b] Chi-squared test. ACS: Acute Coronary Syndrome; non-ACS: non-Acute Coronary Syndrome.

Table 2 examines medical and biochemical characteristics. The groups showed almost similar symptom duration where ACS patients had 3.15 hours of symptoms, and non-ACS patients had 3.22 hours of symptoms (p = 0.8230). Both study groups showed similar hypertension pattern with ACS patients had 58.06%, and non-ACS patients had 55.26% (p = 0.8368). Whereas, the ACS group had a higher diabetes rate (46.77%) than the non-ACS group (26.32%), however, the difference has not showed the statistical significance level (p = 0.0875). The results displayed highly significant dissimilarity in lipid parameters. The ACS group showed total cholesterol levels above normal in 48.39% of patients with the condition, while the non-ACS group showed this condition in only 2.63% of patients (p < 0.0001). Further, the ACS group showed higher levels of LDL levels in 37.10% of patients, whereas the non-ACS group showed none (p < 0.0001). The 58 patients in (93.55%) ACS group demonstrated lower HDL level, compared with 60.53% in the non-ACS group (p < 0.0001). The ACS group exhibited high TG in 79.03% of patients, whereas the non-ACS group showed this pattern in 15.79% of patients (p < 0.0001).

Table 2: Clinical features of patients with acute coronary syndrome.

Characteristics	Study groups		No. (%)	
	non-ACS (n=38)	ACS (n=62)	P value	Significance
Symptom's duration				
1-3 hours.	23 (60.53%)	36 (58.06%)	0.8370[b]	ns
4-6 hours.	15 (39.47%)	26 (41.94%)		
Symptom's duration (mean ± SD)	3.22 ± 1.85	3.15 ±1.60	0.8230[a]	ns
Hypertension				
No	17 (44.74%)	26 (41.94%)	0.8368[b]	ns
Yes	21 (55.26%)	36 (58.06%)		
Diabetes mellitus				
Normal	14 (36.84%)	20 (32.26%)	0.0875[b]	ns
Prediabetes	14 (36.84%)	13 (20.97%)		
Diabetes	10 (26.32%)	29 (46.77%)		
Total Cholesterol				
Desirable level	20 (52.63%)	7 (11.29%)	<0.0001[b]	**
Borderline high	17 (44.74%)	25 (40.32%)		
High	1 (2.63%)	30 (48.39%)		
LDL				
Near optimal	20 (52.63%)	5 (8.06%)		
Borderline high	14 (36.84%)	33 (53.23%)	<0.0001[b]	**
Optimal	4 (10.53%)	1 (1.61%)		
High	0 (0.00%)	23 (37.10%)		
HDL				
Low	23 (60.53%)	58 (93.55%)	<0.0001[b]	**
Optimal	15 (39.47%)	4 (6.45%)		
TG				
Normal	12 (31.58%)	3 (4.84%)	<0.0001[b]	**
Borderline high	20 (52.63%)	10 (16.13%)		
High	6 (15.79%)	49 (79.03%)		

[a] Independent t-test and [b]Chi-squared tests.

Table 3 shows the clinical results and medical symptoms. ACS patients had a 61.29% admission rate to the ward, whereas, non-ACS patients had a 44.74% admission rate, with no statistically significant differences (p = 0.1063). ACS group experienced statistically significant higher rate of dyspnea (96.77%) than the non-ACS group (73.68%; p = 0.0009). Additionally, the patient group with radiation of pain to the arm was 67.74% in ACS patients and 28.95% in non-ACS patients (p = 0.0002). Finally, nausea and vomiting were experienced by 59.68% in ACS cases compared to 26.32% in non-ACS cases (p = 0.0012).

Table 3: Outcomes of patients among ACS and its types.

Outcomes	Diagnosis No. (%)		*P value	Significance
	non-ACS (n=38)	ACS (n=62)		
Admission to the ward				
No	21 (55.26%)	24 (38.71%)	0.1063	ns
Yes	17 (44.74%)	38 (61.29%)		
Required for PCI			N/A	
No	38 (100%)	62 (100%)		
Mortality			N/A	
No	38 (100%)	62 (100%)		
Dyspnea				
No	10 (26.32%)	2 (3.23%)	0.0009	**
Yes	28 (73.68 %)	60 (96.77 %)		
Radiation to the arm				
No	27 (71.05%)	20 (32.26%)	0.0002	**
Yes	11 (28.95%)	42 (67.74%)		
Nausea and vomiting				
No	28 (73.68%)	25 (40.32%)	0.0012	**
Yes	10 (26.32%)	37 (59.68%)		

* chi-squared test was performed for statistical analysis, N/A: not applicable.

Table 4 shows biomarkers levels in the study's group. Both, HS-Troponin and copeptin levels showed minor difference between the ACS and non-ACS groups, however, the difference were not statistically signficant (p = 0.45, P=0.45, respectively). Similarly, the median HS-troponin × copeptin interaction was higher in ACS (3904.63, MAD 3181.23) compared to non-ACS (2885.81, MAD 2280.59), but this result was not statistically significant (p = 0.45).

Table 4: Comparison and role of interaction of HS-Troponin and Copeptin in ACS vs non-ACS subjects.

Study groups	HS-Troponin (pmol/L)		Copeptin (pmol/L)		HS-Troponin*Copeptin interaction	
	Med (MAD)	*P value	Med (MAD)	*P value	Med (MAD)	*p value
ACS (n=62)	15.08 (2.82)	0.94	298.92 (187.92)	0.45	3904.63 (3181.23)	0.45
non-ACS (N=38)	15.49 (2.69)		288.45 (208.32)		2885.81 (2280.59)	

* Mann Whitney U test was implemented to preform statistical analysis.

Table 5 presents the changes in biomarkers across lipid categories within the ACS group. Medians total cholesterol values ranged from 1555.10 to 3774.43, with no statistically significant difference observed (p = 0.6000). Copeptin levels ranged from 165.26 to 329.05 pmol/L, again with no statistically significant difference (p = 0.7148). Additionally, LDL, HDL, and TG concentration did not show statistically significant differences (p>0.05). The HS-troponin was significantly lower in patients with high LDL compared to those with borderline (13.45 vs. 16.11; p = 0.0194). While, the HS-troponin was not statistically significantly different in ACS patients with different total cholesterol, HDL, and TG.

Table 5: Comparisons of HS-troponin*Copeptin int. and Copeptin in ACS patients with different biomedical measurements and differential diagnosis of ACS.

Lipid profile	HS-troponin*Copeptin interaction			Copeptin pmol/L			HS-troponin (pmol/L)		
	Med	MAD	* P value	Med	MAD	* P value	Med	MAD	* P value
Total Cholesterol									
Desirable	1555.1	1331.06	0.6	165.26	143.10	0.7148	14.45	1.51	0.1333
level	3774.43	3192.41		329.05	165.88		16.21	1.97	
Borderline	2987.55	2182.38		253.78	157.45		14.78	2.62	
High									
LDL									
Near optimal	1320.81	761.91		99.66	69.87		17.11	1.65	
Optimal	2987.55	2763.51	0.765	365.23	132.18	0.7735	9.40	0.00	0.0194
Borderline high	4151.03	3345.69		411.23	114.90		16.11	1.77	
High	3683.12	2675.80		253.78	148.38		13.45	2.65	
HDL									
Low	3683.12	2970.17	0.9091	301.51	191.58	0.7819	15.08	2.82	0.9657
Optimal	1335.64	1028.20		106.17	83.16		15.03	2.91	
TG									
Borderline high	3237.9	2555.65	0.3899	308.75	193.41	0.2554	10.82	2.91	0.3768
Normal	1116.19	557.29		99.66	69.87		17.11	1.65	
High	4052.32	3265.85		309.72	172.57		15.15	1.71	

MAD: Median Absolute Deviation; Med: Median

* Kruskal-Wallis test was performed for statistical analyses.

4. Discussion

The primary findings of this study are that traditional demographic and clinical attributes, such as aging, obesity, and pain radiation, linked to ACS. Advanced age consistently emerges as a strong predictor of negative outcomes across study [23], which reflects the cumulative, time-dependent nature of

atherogenesis and impaired smooth muscle cell matrix repair [24]. Additionally, the ACS group presented a substantially elevated obesity rate at 51.6% compared to 23.7% in non-ACS patients, which is driven by viscural and pericoronary adipocyte dysfunction and causing plaque destabilization by chronic local inflammation, indicating that excess BMI is a primary factor contributing to cardiovascular disease [25].

Although no significant differences were noticed among the two groups regarding sex and smoking status, high smoking rates are consistently reported amid the patients visiting emergency rooms and complaining about sudden chest pain [26] as smoking is a recognized determinant for ACS [27]. The similarity in sex distribution aligns with research indicating that males are more frequently diagnosed with ACS than females [28], although female patients often present at high rates and display distinct risk factors and atypical symptoms [29].

When analyzing symptomatic presentation, this study systematically presents symptom profiles, providing critical clinical data. Diagnostic criteria demonstrate that left arm pain in ACS patients, is classified as a "high likelihood" symptom of myocardial ischemia [30]. Furthermore, the presentation of high prevalence of dyspnea in the ACS group is identified in academic literature as a "chest pain equivalent" in acute cardiac care and this could be due to its association with elevated risk scores and increased myocardial damage assessment. This happens by local myocardial hypoxia which forces anaerobic metabolism to releases noxious metabolites to stimulate cardiac sympathetic afferent fibers [31]. The presence of nausea and vomiting in the ACS patients are common symptoms of myocardial infarction because they activate the vasopressin system, which can increase copeptin release [32]. This indicates that stress-related biomarkers increase in the patients with ACS experience without any connection to their level of heart tissue damage [33].

The considerably advanced rates of elevated total cholesterol, LDL, and TG, along with diminished HDL levels in the ACS group demonstrate that dyslipidemia is a fundamental factor that drives atherosclerosis development, leading to ACS [34]. The stark contrast, such as 37.1% of ACS patients having elevated LDL, emphasizes that a pathological lipid profile remains a hallmark of patients who transition from stable coronary disease to acute syndromes by fostering subendothelial LDL and oxidation, which incubates macrophage-mediated inflammation. Although, the ACS group showed higher diabetes rates than others, the diabetes prevalence lacked statistical significance and this could be due to sample size limitations in this study [35].

The biochemical findings about copeptin and its interaction with HS-troponin provide evidence that challenges the DMS, which is frequently advocated in the literature. No significant differences in copeptin levels were noticed among the two studied groups, and similar pattern observed in the HS-troponin × copeptin interaction. Most of the prospective studies and meta-analyses show that AMI and ACS patients have higher copeptin levels than non-ACS patients [36]. The DMS uses copeptin as a biomarker of endogenous stress to cover the "troponin-blind window," which extends from the first hour to the third hour after the initial of symptom onset, because cTn levels remain undetectable during that time [37-38]. Multiple studies demonstrate that combining copeptin and cTn testing improves both sensitivity and negative predictive value for ACS diagnosis at patient presentation [39]. However, the lack of significance in this study's results may be explained by several factors such as sample size, design of the study and timing of the tested performed.

The study's median copeptin level of 290 pmol/L is extraordinarily high. For context, typical diagnostic cut-offs for ruling out ACS range from 10 to 14 pmol/L [36]. The 290 pmol/L level serves as a threshold that medical professionals use to diagnose patients who experience acute physiological shock or severe heart failure. The copeptin levels in both groups reached this extreme level and this could be related to the population experiences extreme systemic stress, which makes the marker lose its ability to identify coronary events [40].

The sources indicate that copeptin provides less additional diagnostic value when high-sensitivity troponin tests replace standard testing methods [41]. The high-sensitivity tests enable detection of extremely small troponin elevations which occurred before the "troponin-blind window" that copeptin was designed to cover [38]. The clinical utility of copeptin must be reconsidered in the context of hs-cTn assays. Historically, copeptin was proposed as a bridge for the 'troponin-blind window', the period

between the onset of ischemia and the detectable rise of standard troponin. However, high-sensitivity assays have noticeably narrowed this diagnostic gap, allowing the detection of myocardial injury at lower concentrations and earlier time points [42]. Consequently, the regular addition diagnostic utility of copeptin is naturally attenuated paired with Hs-cTn, as superior analytical sensitivity of modern assays renders the earlier detection benefits of copeptin less pronounced in clinical practice. This suggests that in hospitals utilizing hs-cTn, copeptin may transition from a primary diagnostic tool to a secondary marker for risk stratification.

The diagnostic accuracy of the copeptin testing depends mostly on the timing of the test. The copeptin test results show an initial rise to its peak levels before it drops back to normal level within 12 to 36 hours of symptom onset [43]. The difference in copeptin levels between the two groups will disappear when the blood samples are collected after the recommended time interval, or when the non-ACS group includes few patients with serious medical conditions such as pulmonary embolism and heart failure [40]. The diagnostic accuracy of copeptin test is mainly time-dependent, governed by its quick release and subsequent clearance kinetics [11]. In this study cohort, diversity in the timing of presentation relative to symptom onset likely influenced the observation of copeptin level. Patients presenting late in the clinical course may face declining levels. In contrast, those presenting very early or those with continuous, chronic stress may face levels that mask the differences between ACS and non-ACS patients [44]. It is important to note that the biomarker's ability to differentiate between acute events and chronic physiological states is significantly weak.

Copeptin has been known as an effective biomarker for acute cardiac diseases [45]. It is still under test in clinical settings due to its vasopressinergic system's sensitivity to physiological requirements [46]. The patients who have participated in this study cohort may not have increased copeptin level due to only myocardial injury. In contrast, other clinical and lifestyle factors can influence, such as chronic cigarette use, diabetes mellitus, high lipid profile, and even hydration level, may also affect copeptine level. Tobacco use or smoking cigarettes is one of a very well-studied lifestyle and habit trigger for the vasopressinergic system which elevated copeptin levels [47]. Nicotine have shown to stimulate the hypothalamic nuclei, which leads to the cosecretion of arginine vasopressin (AVP) [48]. Chronic smokers may have higher baseline copeptin levels [49], which might be due to neurohormonal activation and oxidative stress rather than acute myocardial injury alone.

Further, elevated hemoglobin A1c (HbA1c) levels act as a marker of long-term metabolic dysregulation [50], which significantly acts on copeptin levels. On the other hand, hyperglycemia elevates plasma osmolality and directly triggers activation of the hypothalamic-neurohypophyseal axis to initiate AVP release [51]. Elevated HbA1c causes microvascular damage, particularly nephropathy [52]. Dyslipidemia can be a significant source of variance in circulating copeptin levels [53] beyond its well-established role in atherosclerosis [54]. A high lipid profile can cause long-term, low-grade systemic inflammation, which directly elevates copeptin levels [55]. Regarding the hydration level in the body, it constitutes the most significant physiological determinant of copeptin secretion [56]. As the primary surrogate marker for AVP, copeptins levels are inherently tied to plasma osmolality and fluid homeostasis [57]. Dehydration is the main trigger of osmoreceptor-mediated activation of the hypothalamic-neurohypophyseal axis, leading to upregulation of copeptin independently of myocardial pathology [58].

Patients with high TG levels had significantly lower HS-troponin concentrations than patients with borderline-high TGs, suggesting an inverse relationship between TG elevation and the degree of myocardial injury in ACS. However, no significant associations between HS-troponin and total cholesterol or HDL levels were observed. This can be related to the fact that dyslipidemia may affect the release of cardiac biomarkers and cardiovascular risk profiles differently.

To make sure the copeptins level is accurate within this study cohort, a secondary objective was to establish a localized range of copeptin levels. A cohort of 50 healthy individuals, matched for age and sex distribution, was recruited to characterize baseline copeptin levels in this community. This action was necessary to understand that sociodemographic factors, environmental stressors, and regional lifestyle diversity can have influence on baseline neurohormonal activity [59]. By establishing these localized reference values, this study provides a more accurate, context-sensitive benchmark for

understanding copeptin elevation, rather than depending on standardized range intervals derived from populations with different sociodemographic backgrounds. Thus, this study utilized an internal, community range baseline [60]. The mean copeptin level in healthy individuals was 60.61±23.01 pmol/L. This approach empowers the clinical relevance of the elevated copeptin levels observed in the patient cohort, as it provides a robust, locally derived point of comparison. Moreover, this reduces the risk of reference range bias and enhancing the reliability of the study's findings, which highlights the critical role of geographical, dietary, and lifestyle factors in shaping the physiological 'normal' for neurohormonal markers. We argue that for copeptin to be used effectively in regional diagnostic algorithms, medical institutions must pivot toward establishing internally validated, population-specific reference intervals rather than adhering to firm and externally generated cut-offs that may not reflect the baseline stress load of the local patient population.

The study provides evidence that in high-stress, comorbid cohorts, the diagnostic specificity of copeptin is masked by the systemic metabolic load. The combination of troponin and copeptin biochemical testing results has greater clinical value than traditional ACS diagnostic symptoms, such as arm radiation and dyspnea [61]. The ACS group exhibits significant lipid abnormalities, which demonstrate that this patient population requires intensive metabolic treatment. The two groups showed identical admission rates, which demonstrated that triage continues to face difficulties because non-ACS patients need hospitalization for serious medical conditions which produce similar stress levels and biomarker increases. Elevated HbA1c levels serve as a marker of long-term metabolic dysregulation, which significantly influences copeptin levels.

5. Conclusions

The study demonstrates a high prevalence of traditional risk factors and symptoms, including older age, obesity, and pain radiation, within the study population. The study proves that HS-troponin and copeptin interaction and the biomarkers alone do not have universal use across different situations. The specific group studies showed that copeptin and HS-troponin, and their interaction could not differentiate between ACS and non-ACS cases because the combination of high background systemic stress and modern troponin tests, which detect even minor stress, rendered all stress biomarkers useless. Future studies will require greater emphasis on clinical risk scores and lipid profiles, as these factors will help improve ACS diagnosis when biochemical markers are inconclusive.

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